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Clinical development of curcumin in neurodegenerative disease

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Summary

Curcumin, a polyphenolic antioxidant derived from the turmeric root has undergone extensive preclinical development, showing remarkable efficacy in wound repair, cancer and inflammatory disorders. This review addresses the rationale for its use in neurodegenerative disease, particularly Alzheimer's disease (AD). Curcumin is a pleiotropic molecule, which not only directly binds to and limits aggregation of the β -sheet conformations of amyloid characteristic of many neurodegenerative diseases but also restores homeostasis of the inflammatory system, boosts the heat shock system to enhance clearance of toxic aggregates, scavenges free radicals, chelates iron and induces anti-oxidant response elements. Although curcumin corrects dysregulation of multiple pathways, it may exert many effects via a few molecular targets. Pharmaceutical development of natural compounds like curcumin and synthetic derivatives have strong scientific rationale, but will require overcoming various hurdles including; high cost of trials, concern about profitability and misconceptions about drug specificity, stability and bioavailability.

Keywords

Alzheimer's Disease; amyloid; amyloid-binding; antioxidant; Activator Protein 1; brain derived neurotrophic factor; c-jun N terminal Kinase; Heat shock proteins; misfolded proteins; Neurodegeneration; neuroinflammation; Non-steroidal anti-inflammatory drugs; Nuclear Factor Kappa B; Polyphenolic antioxidants

I. Introduction

Here we will review the rationale for the use of curcumin relevant to AD and related neurodegenerative diseases, focusing on curcumin's amyloid binding effects, antioxidant and anti-inflammatory activities, effects on neurogenesis and neuroprotection as well as its

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effects on the heat shock protein system important for removal of misfolded proteins. It is also referred to as a ‘hormetic phytochemical’ because it activates adaptive stress response signaling pathways that increase cellular resistance to injury and disease [1]. Prior reviews summarize some of the key details related to Alzheimer’s in more depth [2-5].

For over 4,000 years, practitioners of Ayurvedic and traditional Chinese and Southeast Asian medicine have identified and used turmeric root extracts as a food preservative and for culinary, religious and medical conditions. Curcumin, the major active component of turmeric, is a biphenolic anti-inflammatory and antioxidant molecule that has shown exceptional promise as a chemopreventive and chemosensitizer in many cancers, inflammatory disorders and in models of Alzheimer’s (AD) and other neurodegenerative disorders.

Asian countries typically ingest the highest intake of turmeric, with up 1 gram of turmeric, which can contain from 60 to 200 mg of curcumin. A cross national epidemiological (Indo-US) study comparing rural populations in Northern India (n = 4,450) and southwestern Pennsylvania (n = 886), showed a lower incidence and prevalence of AD in India [6,7] even after correction for E4 isoform [8], despite a greater than 25% prevalence of metabolic syndrome a major AD risk factor. The Delphi Consensus study similarly showed a low prevalence in South Asia [9], but more detailed analysis showed that this protection is limited to rural areas, as urban populations in India showed considerable increased risk relative to rural Indian populations and no differences in incidence [10].

We discuss current problems in drug development, including proprietary formulations and conflicting information about its bioavailability, stability and activity of parent versus conjugated forms.

II. Curcumin binds to the β -pleated sheet of A β , tau and other amyloid proteins in the brain and retina

A prominent feature of neurodegenerative diseases is protein dyshomeostasis characterized by accumulation of misfolded protein aggregates within (e.g. tau from neurofibrillary tangles) and outside of cells (e.g. neuritic β -amyloid plaques). Curcumin’s ability to bind to the β -pleated structure of amyloids is one mechanism by which it reduces plaque burden in most AD models of plaque pathogenesis [11-13]. Structurally, curcumin is similar to amyloid binding probes like Congo Red and Chrysamine G, which bind to positive charges on amino acid chains of every 4 of beta-pleated sheets (spanning 19 Å or distance between four beta pleated sheets). Curcumin can bind A β and reduce toxic aggregates by modulating aggregation [13-15]. Curcumin’s diketone bridge is essential for amyloid binding and plaque reduction, but is not essential for curcumin’s anti-inflammatory effects since reduced curcumin (tetrahydrocurcumin) retains potent anti-inflammatory effects [16]. Curcumin also reduces A β aggregates in APP^{sw} models with the dominant mutation Presenilin 1, but not necessarily amyloid burden, but novel curcumin derivatives with substitutions at C4 can reduce amyloid deposition in these aggressive models [17].

Because of curcumin's natural fluorescence, it may be useful to monitor disease progression, particularly via analysis of retinal plaques, which may mirror brain plaque deposition. After oral gavage with curcumin, Curcumin fluorescence is apparent in the retinal plaques of APP transgenic mice, which may serve as a non-invasive clinical diagnostic or surrogate biomarker [18], now being testing in the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) study [19]. The binding affinity of curcumin for A β aggregates is as high or higher than successful molecular imaging probes such as PIB in FDG PET, with a K_i of 0.07 nM for F18 labeled curcumin binding for fibrillar A β [20]. Curcumin analogues such as CRANAD-17 and CRANAD-58 are being developed that may be particularly useful in live fluorescence imaging of plaques [21].

X-ray microcrystallography of fiber forming segments of tau with small molecule binders identify curcumin as a pharmacophore, binding to the β -pleated sheet in the paired helical filaments of tau [22]. Curcumin binds to neurofibrillary tangles (NFTs) in human AD brain and animals [23,24]. Some high throughput screens have identified curcumin and related polyphenols as significant tau aggregation inhibitors [25]. In pure tauopathy models, oral curcumin reduces soluble pTau oligomers without impacting insoluble tau and corrects synaptic deficits [26]. Curcumin binds other β -pleated sheet structures including aggregates of huntingtin [27] prion [28] and α -synuclein [29-31]. In *Caenorhabditis elegans* with human tau mutations, curcumin improves coordinative movement, reduces neuritic abnormalities, while other compounds reported to clear tau (trehalose and methylene blue) had no favorable effect [32].

III. Neurodegeneration related HSPs defects are corrected by curcumin

Major routes for the removal of toxic protein aggregate are through the ubiquitin proteasome system and the autophagy-lysosomal pathways. Heat shock proteins (HSPs) are molecular chaperones that are important for refolding or degrading misfolded proteins, including amyloidogenic proteins or reducing the risk of formation of toxic oligomeric assemblies of A β , tau, Huntingtin or α -synuclein etc., in addition to promoting ubiquitination and degradation of those aggregates. Efficiency of this system is associated with longevity and the associated genes have been coined the Vitagene system, which includes the cytoprotective heat shock proteins (Hsp) Hsp70 and or Hsp32, also known as heme oxygenase-1 (see Section VI) [33].

Curcumin directly interacts with HSP90 and increase HSP70 and other HSPs and their client proteins in A β -infused rats and in human tau transgenic mice where it reduces tau oligomers [26]. We show that across multiple amyloid models, curcumin corrects transgene-dependent reductions in levels of Hsp90, Hsp70, Hsc70, Hsp60, Hsp40, and their client proteins such as FKBP51, Cdc37, P23 (unpublished observations Frautschy, Cole and Maiti). These effects were observed across multiple amyloid models, suggesting high specificity of curcumin for molecular chaperones involved in protein homeostasis.

IV. Stimulation of phagocytic A β clearance (M2 activation and attenuation of aberrant chronic inflammation (M1 activation))

Turmeric has been used for thousands of years to treat inflammatory disorders and for wound repair. It is a homeostatic regulator of inflammation, attenuating chronic aberrant inflammation (M1 activation) and stimulating resolution of inflammation (M2 activation, Figure 1), but whether it acts on one or multiple transcription factors, receptors or oxygenases is unknown.

Similar to the amyloid vaccine, curcumin increases the association of phagocytic cells with plaque structures and stimulates clearance of A β aggregates in various human cell and rodent AD models [34-36]. The amyloid vaccine can be associated with microhemorrhages and vasogenic edema, which can be visualized clinically in MRI as amyloid-related imaging abnormalities (ARIA) [37], but it has not been demonstrated if curcumin has this effect. Although curcumin is protective in mouse models of intracerebral hemorrhage curcumin [38], potential adverse effects need to be examined in a vascular amyloid model.

Curcumin also reduces chronic inflammation while promoting resolution of inflammation including in AD models [34,36,39]. Curcumin reduces elevations in the inflammatory cytokines Interleukin 1 β and TNF α in the Tg2576 AD mouse model [40].

Curcumin is an inhibitor of NF κ B and the Activator Protein 1 (AP1) [41-43]. Pathways associated with these transcription factors are dysregulated in AD, limiting inflammatory resolution. Curcumin reduces AP1 transcription by reducing the upstream hyperactivation of the tau kinase JNK that will also reduce hyperphosphorylated tau.

Data suggest curcumin interferes with the homodimerization of the TLR4 receptor complex that is responsible for NF κ B activation [44], which limits PPAR γ activation. Curcumin also increases PPAR γ expression [45], but it is not clear if it can do so directly. PPAR γ forms heterodimers with RXR alpha to regulate microglial activation and phagocytosis [46]. PPAR γ will downregulate inflammatory cytokines that contribute to tau kinase hyperactivity, ptau accumulation and oxidative damage.

The mechanism of curcumin in the homeostatic regulation of inflammation likely includes inhibition of p300 histone acetyltransferase (HAT) activity, which it does so at picomolar levels, far below levels needed to inhibit NF κ B activation. This acetyltransferase acetylates and stabilizes NF κ B to further contribute to chronic inflammation, and counteracts deacetylases like sirtuins that can resolve inflammation. Since hyperacetylation plays a role in pathogenesis of many disorders, P300 HAT inhibitors are being developed for heart myopathy, HIV, cancer and other disorders. In addition to the effects of hyperacetylation in inflammatory disease, hyperacetylation of tau contributes to tau aggregation [47]. Therefore p300 HAT inhibition may be one of the significant targets of curcumin against both tau and inflammation pathways in AD pathogenesis.

Curcumin limits arachidonic acid (AA) substrates and aberrant inflammatory cytokine production. Curcumin does not directly inhibit cyclooxygenase except at high concentrations

(50-100 μ M) [48]. However, it alters multiple AA metabolites by reducing the induction of cyclooxygenase-2 and inhibits 5-lipoxygenase (IC₅₀ ~ 0.7 μ M), while suppressing the phosphorylation and activation of cytosolic phospholipase A2 [49].

Curcumin can directly reduce A β production by inhibiting the activity of β -secretase BACE, the N terminal cleavage of the transmembrane amyloid precursor protein (APP) [50], but may also indirectly reduce BACE by attenuating its proinflammatory upregulation [51]. It also may reduce A β production by inhibiting GSK3 β -mediated PS1 activation [52] or lowering A β levels by attenuating the maturation of APP in the secretory pathway [53].

V. Modulating of aberrant tau phosphorylation and acetylation

Curcumin reduces accumulation of soluble tau aggregates, a major cause of synapse loss. It does so via multiple actions. It reduces ptau by directly reducing the activation of tau kinase such as c-Jun N terminal kinase (JNK) and GSK3 β in neurons and by reducing glial produced inflammatory cytokines that activate neuronal tau kinases. Further it reduces oxidation of tau that promotes its activation and can reduce acetylation of tau via effects on CBP/p300 HAT. It can promote HSPs responses that selectively remove soluble tau oligomers associated with cognitive and synapse loss.

VI. Curcumin's antioxidant activity and induction of antioxidant response elements (AREs)

Structurally, curcumin's two methoxyphenol groups linked by a β diketone bridge confers both metal chelation and Michael acceptor activities [54]. Curcumin scavenges superoxide and hydroxyl radicals, conserves glutathione (GSH) levels and decreases the concentration of circulating free radical end products in mouse models and humans [55,56]. Increased oxidative stress in AD by A β , tau or inflammation may cause protein oxidation, lipid peroxidation, DNA oxidation and neuronal cell death. We have shown that curcumin effectively protects against DNA oxidative damage in the Tg2576 mouse [57] and lipid peroxidation in an A β -infusion rat model [34].

Like many phytochemicals, curcumin is a phase II inducer [58] that upregulates defense enzymes. Curcumin is a selective Nrf2-Keap1-ARE activator, providing protection against various forms of stress, leading to the increase in activity of heme oxygenase-1 (HO-1), a redox-sensitive inducible protein [59]. Curcumin increases HO-1 in astrocytes and neurons where it mediates neuroprotection against oxidative stress [60]. Increases in astrocytes can improve outcome after stroke [61]. HO-1 is oxidized in AD and MCI brain and has been implicated in insulin resistance, a major AD risk factor [62]. Induction of ARE [63] also increases glutathione biosynthesis [64], and the activity of c-glutamyl-cysteinyl synthetase and other GSH-linked detoxifying enzymes [65] as well as human glutathione S-transferase P1 expression [66].

Curcumin can also limit oxidation by its action as a copper and iron chelator [54,67]. Reports shows that the transition metals iron and copper, which accumulate excessively in the brains of AD, PD, and other neurodegenerative diseases induce genotoxic ROS and

inhibit DNA damage repair. Curcumin with both chelating and reducing activities reverses their binding [68]. Curcumin also attenuates aluminum-induced oxidative stress and mitochondrial dysfunction in rat brain [69].

VII. Insulin signaling “type III diabetes”

Insulin signaling defects are observed in AD brain and insulin resistance associated with type II diabetes mellitus is a risk factor for AD [70]. In AD subjects, there are deficits in glucose metabolism [71] corresponding to reductions in insulin signaling [72,73]. Curcumin can enhance insulin signaling by stimulating Akt and reducing GSK3 β activation [26]. It can also regulate insulin signaling in part by inhibition of JNK that phosphorylates Insulin Receptor Substrate (IRS) [74]. IRS is an adaptor protein linked to insulin resistance in AD and in diabetes animal models [75]. Treatment of 3xTg-AD mice with curcumin significantly suppressed a JNK/IRS-1/tau signaling pathway that leads to AD-like p-IRS-1/insulin signaling defects, providing an additional mechanism for efficacy in an AD model with tau pathology, particularly in combination with fish oil [74].

VIII. BDNF and Neurogenesis

Curcumin at low but not high concentrations stimulated neurogenesis and the proliferation of adult hippocampal progenitor cells [76]. It has been demonstrated that curcumin nanoparticles induced neurogenesis in an AD model by suppression of the Wnt/beta catenin signaling pathway regulating GSK3 β activity [77]. A related potential mechanism is via promoting brain-derived neurotrophic factor (BDNF) expression which regulates neurogenesis [78]. Curcumin has been shown to restore BDNF function after brain trauma [79] and a curcumin pyrazole derivative CNB-001 stimulated BDNF and improved memory [80].

IX. Reliability of pharmacokinetic Studies in predicting efficacy

Curcumin's development clinically has been slow, likely related to concerns over poor bioavailability, poor water solubility at neutral or acid pH, instability at basic pH and rapid intestinal and first pass glucuronidation. Initial attempts to evaluate curcumin levels in humans demonstrated no detectable levels of the parent compound in the plasma unless patients ingested more than 8 g [81]. Other clinical pharmacokinetic studies confirmed nondetectable plasma levels of parent compound and its extensive glucuronidation and sulfation [5,82-84]. These and other studies show that high levels of glucuronidated or sulfated curcumin are achieved without formulation [83,85,86], and even though these conjugates will not readily penetrate the brain, they may exert beneficial effects on peripheral inflammation, such as has been reported with the Meriva formulation [87]. However, Theracurmin is being tested to examine effect on biomarkers in MCI (NCT01383161) and did not show any effect on inflammatory cytokines in a Phase I cancer trial [88].

Curcumin molecules that bypass intestinal conjugation, are still likely to quickly be conjugated by first pass metabolism in the liver within 3 to 6 hours, yet this may be sufficient to allow delivery to lipid tissue like the brain where it remains stable and can even

accumulate with frequent ingestion. Traditionally curcumin pharmacokinetic studies have used one-compartment model (V1) and show rapid first pass metabolism, but because curcumin, like other lipophilic drugs, can accumulate at different rates in different tissues and have different stability in different tissues, two (V2) or three (V3) compartment models are likely to yield more clinically useful information.

IX. Commercial Formulations

New formulations being developed for improved bioavailability rely on measurement of plasma levels of glucuronidated curcumin to assess quality, but it is unclear if this meaningfully reflects brain tissue levels, particularly since high levels of parent compound accumulating in the brain can occur in the absence of detectable levels in the blood [16]. Although we have established that curcumin is more stable in the red blood cell (RBC) compartment than plasma and that levels of curcumin in the RBC parallel levels in the brain (unpublished observations), standardizing better methods are paramount to predicting neuroprotection in humans.

Although several new formulations have been developed, there has not been an adequate side-by-side comparative efficacy and PK studies comparing formulations. Meta-analyses are unlikely to yield reliable comparisons, since each study uses different methods of analysis and different experimental design and different methods of delivery. One major problem in comparing formulations done at different times and institutions is differences in the blood storage and preparation, since there is still rapid ex vivo metabolism, glucuronidation and/or hydrolysis of curcumin, so methods of sample preparation need to be standardized, such as the need to add 5% phosphoric acid to plasma to prevent hydrolysis [89]. Another major problem in extending rodent studies to humans is the diluents for new formulation gavage studies are in themselves a form of formulation (e.g. cyclodextrins, deoxycholates, Chremophor, olive oil) making them confounders to assess new formulations. Further, in addition to fasting that increases absorption, effects of high protein, fat or carbohydrate and gender on absorption

The first curcumin formulation developed was Curcumin Bioperine (Sabinsa, [90] which included a molecule in black pepper, piperine, a glucuronidation inhibitor. Since alkalinity increases absorption [91], piperine's alkalinity may instead or also contribute to the improved absorption. Biocurcumin or BCM-95 is a curcumin extract, with essential oils added back in and proposed to increase bioavailability [92]. Theracurmin [88] is another novel formulation with 10% curcumin, 38% water, 46% glycerin, 4% gum ghatti, which is a polysaccharide emulsifier and thickener.

Our group was involved in development of Curcumin Longvida, a solid lipid nanoparticle, which did show detectable levels of parent compound "free or unconjugated curcumin" in a human PK study [93], but whether this formulation is superior to other formulations on the market has not established. NIH funded the development of this curcumin formulation to improve efficacy in AD models. The final product was then licensed by UC Regents to Verdure Sciences (Indianapolis, IN) as Longvida Curcumin. It has undergone extensive safety testing in animals which showed that the Observed-Adverse-Effect Level (NOAEL)

for this standardized novel curcumin preparation given for 90 days was 720 mg/kg bw/day (5760 ppm), the highest dose tested [94]. There were small significant and gender-dependent changes in eosinophils, bilirubin, urea and neutrophils, but all changes were still in the mid-range of normal.

X. Curcumin Safety and Trials for cognition

Curcumin has undergone extensive toxicology testing because of its chemopreventive activities showing that long term use of doses 5,000 ppm or below are safe [95]. Further turmeric oleoresin (85% curcumin) is on the FDA GRAS list. Although none of the trials have shown any evidence of significant toxicity, some changes were observed leading to concerns of potential toxicity. One 6-month trial demonstrated no evidence of liver toxicity, since although ALT/GPT (alanine aminotransferase /glutamic-pyruvic transaminase levels) were higher at baseline in subjects to be given low dose curcumin neither dose of curcumin showed any changes from baseline [96]. In this same study curcumin did not increase triacylglycerols, total, LDL or cholesterol over 1 month or 6 months. Although total cholesterol correlated positively with plasma glucuronidated curcumin, this corresponded to increases in HDL, particularly in the 1 g group where HDL increase 0.27 mM and LDL reduced 0.12 mM in response to curcumin. Importantly these patients were not hypercholesterolemic to begin with nor did they become hypercholesterolemic. Similarly no toxicity was observed in a similar AD trial [85].

Despite the excellent safety profiles of curcumin, neither study showed any changes on cognitive endpoints [83,85]. However in the Baum study there was a trend ($p < 0.11$) for increased plasma levels of Aβ40, which could indicate clearance out of the brain. That lack of efficacy could be due to 1-that high conjugated curcumin but not the parent compound was detected in plasma, suggesting levels are too low for adequate brain delivery or 2- that the treatment of 6 months was of too short duration or 3-curcumin is not effective after the onset of disease.

In another study three patients with advanced stage dementia were given turmeric capsules with bioavailable curcumin (equivalent to 764 mg turmeric and 100 mg/day of curcumin) over a one-year period, and patients showed improvement in neuropsychiatric inventory scores and cognition and reduction in caregiver burden [97].

Current approaches are to intervene earlier prior to disease onset. There are two ongoing trials for subjects with MCI at University of California, Los Angeles and the Veterans Administration to be completed in 2016 or 2017. First, Theracurmin is being tested in an 18-month study at 30 mg curcumin/day (465 mg Theracurmin) (NCT01383161). Second, Longvida is tested in a 12-month study in MCI subjects, using a dose of 4 g per day (equivalent to 800 mg/day curcumin) for effects on and plasma inflammatory biomarkers and cerebral metabolism using FDG PET imaging (NCT01811381).

Curcumin is also being considered for prevention. To date there have been two completed trials in the cognitively normal geriatric population, using Longvida, at 400 mg per day (equivalent to 80 mg/day curcumin) showing positive but small effects on plasma

biomarkers in a middle aged population [98] and on cognition and mood in an elderly population [99].

Finally acute dosing of Longvida is being used in the AIBL program as a non-invasive biomarker for retinal plaques to determine if it parallels the PET amyloid probes [19].

Expert commentary

Alzheimer's disease is a complicated syndrome of aging with a decades-long prodromal period of accumulation of A β and tau pathology accompanied by oxidative damage and inflammation, which develops before an insidious clinical onset. These factors can also act independently to cause neuronal damage and cognitive deficits, arguing against benefits of single drug targets for neurodegenerative disease. Curcumin is a safe and inexpensive pleiotropic agent that is a promising candidate to act upon multiple aspects of the disease process. Although the most relevant molecular targets are uncertain, its effect on binding amyloid and maintaining inflammatory and protein homeostasis are critical for observed benefits in AD models. A comparison of current formulations in clinical trials is warranted, and short trials that can determine doses to achieve efficacious target blood levels.

Five-year view

Many obstacles limiting the clinical development of curcumin (and other promising natural compounds) are likely to be overcome with foundation or government funding for comparative efficacy studies. As we come to terms with decades of research and failed trials with single molecular target strategies, finding therapies based on genetic triggers are likely to take a back burner, particularly for prevention or early stage therapeutic drug development. Taking a front seat will be multiple targets to correct dysregulation of multiple signaling pathways, extensive amyloid and tau seeding and] stimulate repair mechanisms with both pharmacological as well as non-pharmacological methods (cognitive and exercise therapy). These therapies will be designed to both target precipitating factors as well as downstream signaling hubs that can remain autonomously dysregulated. Pleiotropic compounds like curcumin that affect multiple targets in the disease can simplify trial design, minimizing the number of drugs needed to alter the disease course. The overhaul of current trial designs will reduce their enormous cost, including incorporation of adaptive trial designs, and more rigorous shorter trials designed to improve strategies to optimize dosage and identify whether drug efficacy may be dependent on ApoE isoform- or gender. Hopefully, these shorter trials will use newly identified surrogate plasma biomarkers as primary outcomes that can be used to increase likelihood of success in prevention trials. Congress will approve increased funding for translational research in Alzheimer's, and pharmaceutical companies will devise strategies to make development of natural compounds profitable. Pleiotropic compounds, are likely to become an important component of treatment and prevention paradigms for AD, but like CVD, a cocktail of drugs and natural supplements like docosahexaenoic acid and fisetin, a cognitive enhancer will be needed to dramatically change the disease course.

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Abbreviations

AIBL	Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing
AA	arachidonic acid
AD	Alzheimer's Disease
Aβ	β -amyloid peptide
AP1	Activator Protein 1
APP	Amyloid precursor protein
ARE	antioxidant response element
BDNF	brain derived neurotrophic factor
CNS	central nervous system
CREB	cyclic adenosine monophosphate response element-binding protein
FDG PET	Fluorodeoxyglucose (18F) positron emission tomography
GSH	glutathione
GSK3β	Glycogen Synthase Kinase 3 β
Hsp	Heat Shock Protein
HAT	p300 histone acetyl transferase
HO	Heme-oxygenase, Hsp32
IRS	Insulin Receptor Substrate
JNK	c-jun N terminal kinase
MCI	Mild Cognitive Impairment
Nrf2	Nuclear Factor-Erythroid 2-related factor 2

NFκB	nuclear factor κ-light-chain-enhancer of activated B cells, transcription factor
PK	Pharmacokinetics
PPAR	Peroxisome proliferator-activator receptor
ROS	reactive oxygen species

Key issues

- Curcumin affects both causal and downstream mediators in Alzheimer's disease pathogenesis and stimulates repair mechanisms but has not been adequately developed clinically.
- Curcumin is an amyloid-binding probe, which reduces chronic inflammation and facilitates resolution of inflammation and reduces lipid peroxidation that correlates with synapse loss.
- For age related diseases like Alzheimer's, which have long prodromal periods and multiple dysregulated signaling pathways, pleiotropic molecules may be more effective than highly specific drugs.
- Although medicinal chemistry and high throughput screening using multiple culture or *C. elegans* or *Drosophila* model systems will likely lead to better treatments in upcoming decades, there needs to be a concerted effort to identify current FDA approved or natural GRAS list compounds that can be quickly and affordably brought to the clinic.
- Government and private funds dedicated to translational research are insufficient, which make it virtually impossible to identify dose, gender, and ApoE isoform dependent effects of drugs with limited patent protection, including curcumin.
- Increase funding for translational research in Alzheimer's is necessary, and for the pharmaceutical industry to envision development of natural compounds as a profitable approach, as has been the case for many natural compounds beginning with aspirin.

Figure 1. Curcumin is a pleiotropic molecule correcting dysregulation of pathways in Alzheimer' models

Pleiotropic actions of curcumin that could exert neuroprotection, neural repair, remove misfolded proteins in multiple neurodegenerative diseases.